

diblock copolymer of formula (XX) (polyoxyethylenepolypropyleneimine/butyleneimine, where i was 44 and j was 9-10). The complexes were prepared by the procedures described in Example 6. The oligonucleotide concentration in the complex or in the free state was 0.17 OD<sub>260</sub>/μl. The copolymer was present in the concentration sufficient to define a ratio of polycation block imino and amino groups to oligonucleotide phosphate groups of 10.

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On page 62 line 10, after "Antisense Oligonucleotide Designed to Inhibit Herpes Virus"

This experiment used a 12-chain oligonucleotide, which had been covalently modified at its 5' end with undecylphosphate substituent and at its 3' end with an acridine group, was used. This oligonucleotide modification has been described by Cho-Chung *et al.*, *Biochemistry Int.*, 25:767-773 (1991). The oligonucleotide sequence utilized, CGTTCCTCTGU, (SEQ ID NO 4) was complementary to the splicing site at 983-994 of the Herpes Simplex Virus 1 ("HSV-1"). As a control, an equivalently modified sequence (AGCAAAGCAGG) (SEQ ID NO 5) complementary to the RNA produced by influenza virus was utilized. The oligonucleotides were applied to HSV-1 infected cells in either the complexed or the free state. When a complex was utilized, the complex was formed with the diblock copolymer of formula (XIX) (polyoxyethylene-poly(L-alanine-L-lysine), wherein i was equal to 44 and j was equal to 8). Oligonucleotide complexes were formed as described in Example 6.

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On page 65, line 6, after "Plasma Life of Polynucleotide Complex"

A<sup>32</sup>P-labelled 17-mer (GGCTCCATTCTTGCTC) (SEQ ID NO 6) complementary to the transcription initiation site of the HIV-1 tat gene was utilized in this example. The oligonucleotide was modified at its 5'-end with cholesterol as described by Boutorin *et al.*, *Bioconjugate Chemistry*, 2: 350-356 (1990). A polynucleotide conjugate of the oligonucleotide was formed with the block copolymer of formula (XX) polyoxyethylene-poly (propyleneimine/butyleneimine), wherein i was 44 and j was 9 to 10). The concentration of the stock solution (dissolved in PBS) of complex was 0.18 OD<sub>260</sub>/μl.

0.75 OD<sub>260</sub>/μl oligonucleotide. The ratio of polycation imino and amino groups to polynucleotide phosphate groups was about 50. The mixture was incubated for one hour at room temperature to allow for the formation of the complex. Then, the complex was purified by gel filtration chromatography on Sephadex G-25 using 0.05 M NaCl as the eluent. The resulting solution of complex exhibited a concentration of 0.11 OD<sub>260</sub>/μl of oligonucleotide. A comparable solution of uncomplex oligonucleotide was prepared. An aliquot of murine blood plasma (10 μl) was mixed with an equal volume of oligonucleotide complex solution or a solution of free oligonucleotide. Samples were incubated at 37°C for various time periods. To stop the reaction of the oligonucleotides with enzymes in the plasma, the samples were diluted with water and extracted with a water-saturated mixture of phenol:chloroform (1:1). The aqueous phase of the extraction was isolated, and the oligonucleotide therein was precipitated with 3% lithium Perchlorate. The precipitate was washed with acetone, and then dissolved in 100 μl of water. The presence of undergraded oligonucleotide was determined by high performance liquid chromatography using a C<sub>18</sub>-Silasorb column (4x90mm, Gilson, France) and a gradient of acetonitrile in 0.05 M triethyl-ammoniumacetate (pH 7.0) as the eluent. The results were as follows:

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On page 61, line <sup>10</sup>12, after "Antisense Cell Incorporation Efficiencies"

This experiment examined the effectiveness of "anti-MDR", an antisense molecule comprising a 17-chain oligonucleotide of sequence CCTTCAAGATCCATCCC (SEQ ID NO 3) complementary to positions 422-438 of the mRNA encoding the MDR1 gene product, in reversing multi-drug resistance in SKVLB cells. SKVLB cells are multi-drug resistant cells derived from a ovarian cancer cell line. The MDR1 gene has been identified as responsible for the multi-drug resistance in SKVLB cells. Endicott and Ling, *Ann. Rev. Biochem.*, 58:137 (1989). In particular, the efficiency of the anti-MDR oligonucleotide in the polynucleotide complex of the invention and when in the free state was compared. As controls, the free and completed form of the anti-tat oligonucleotide described above were also used. The polynucleotide complexes were formed with the

CLEAN COPY OF AMENDED SPECIFICATION

One page 49, third paragraph

The p65 subunit of NF- $\kappa$ B (also known as RelA, NF $\kappa$ B3 and NF- $\kappa$ B p65 subunit) is a member of the Rel/NF- $\kappa$ B family of transcription factors which includes p50, cRel, p52 and RelB. NF- $\kappa$ B p65 subunit was first isolated from Jurkat T cells using a probe that spanned a conserved domain to the proto-oncogene cRel (Ruben *et al.*, *Science*, 1991, 251, 1490-1493) and since that time, a naturally occurring transforming variant of the protein has been shown to exist (Narayanan *et al.*, *Science*, 1992, 256, 367-370). In addition, the NF- $\kappa$ B binding DNA sequence has been found in various genes and it has been shown that it is actually important for the expression of the function of genes. The binding sequence of NF- $\kappa$ B ( $\kappa$ B motifs) is composed of about 10 bases having a common sequence which starts with a cluster of G (guanine) and ends with a cluster of C (cytosine) (consensus sequence 5'-GGGRNNYCCC-3'). (SEQ ID NO 1) However, a number of sequences to which DNA binding proteins can be bonded are present on the genes of interleukin- 1 (to be referred to as IL-1 hereinafter in some cases) and tumor necrosis factor (to be referred to as TNF hereinafter in some cases) which are known as inflammatory proteins, and it is known that the NF- $\kappa$ B binding sequence is also present therein (Clark, B. D. *et al.*, *Nuci. Acids Res.*, 14, 7898, 1984; Nedospasov, S. A. *et al.*, *Cold Spring Harb. Symp. Quant. Biol.*, 51, 611, 1986). It has been reported that the binding of NF- $\kappa$ B inhibits transcription to mRNA (Hiscott, J. *et al.*, *Mol. Cell. Biol.*, 13, 6231, 1993; Collart, M. A. *et al.*, *Mol. Cell. Biol.*, 10, 1498, 1990).

On page 59, line 17, after "Oligonucleotide Stabilization"

For this example, a complex containing an oligonucleotide complementary to the transcription initiation site of the HIV-1 tat gene ("anti-tat", comprising GGCTCCATTTCTTGCTC) (SEQ ID NO 2) was prepared using the diblock copolymer of formula (XIX) (polyoxyethylene-poly(L-alanine-L-lysine), wherein i is 44 and j is 8). The oligonucleotide complex was prepared in PBS Buffer (pH 7.0) at a concentration of